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ORIGINAL REPORT

Anterior Hypopituitarism in Adult Survivors of Childhood Cancers Treated With Cranial Radiotherapy: A Report From the St Jude Lifetime Cohort Study

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ABSTRACT

Purpose
To estimate the prevalence of and risk factors for growth hormone deficiency (GHD), luteinizing hormone/follicle-stimulating hormone deficiencies (LH/FSHD), thyroid-stimulatin hormone deficiency (TSHD), and adrenocorticotropic hormone deficiency (ACTHD) after cranial radiotherapy (CRT) in childhood cancer survivors (CCS) and assess the impact of untreated deficiencies.

Patients and Methods
Retrospective study in an established cohort of CCS with 748 participants treated with CRT (394 men; mean age, 34.2 years [range, 19.4 to 59.6 years] observed for a mean of 27.3 years [range, 10.8 to 47.7 years]). Multivariable logistic regression was used to study associations between demographic and treatment-related risk factors and pituitary deficiencies, as well as associations between untreated deficiencies and cardiovascular health, bone mineral density (BMD), and physical fitness.

Results
The estimated point prevalence was 46.5% for GHD, 10.8% for LH/FSHD, 7.5% for TSHD, and 4% for ACTHD, and the cumulative incidence increased with follow-up. GHD and LH/FSHD were not treated in 99.7% and 78.5% of affected individuals, respectively. Male sex and obesity were significantly associated with LH/FSHD; white race was significant associated with LH/FSHD and TSHD. Compared with CRT doses less than 22 Gy, doses of 22 to 29.9 Gy were significantly associated with GHD; doses ≥ 22 Gy were associated with LH/FSHD; and doses ≥ 30 Gy were associated with TSHD and ACTHD. Untreated GHD was significantly associated with decreased muscle mass and exercise tolerance; untreated LH/FSHD was associated with hypertension, dyslipidemia, low BMD, and slow walking; and both deficits, independently, were associated with with abdominal obesity, low energy expenditure, and muscle weakness.

Conclusion
Anterior pituitary deficits are common after CRT. Continued development over time is noted for GHD and LH/FSHD with possible associations between nontreatment of these conditions and poor health outcomes.

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INTRODUCTION

Endocrine complications are among the most commonly diagnosed chronic conditions in childhood cancer survivors (CCS).[1,2] Recent reports have highlighted the increase in their prevalence with time and a relatively high proportion of diagnoses uncovered by systematic risk-based screening.[1,3,4] The risk of anterior pituitary dysfunction in CCS treated with cranial radiotherapy (CRT) is known to increase in a time- and dose-dependent fashion.[5-7] Nevertheless, extended long-term follow-up data are scarce,[1] and the impact of potentially undiagnosed and/or untreated deficiencies on overall health is unknown. One of the primary objectives of the St Jude Lifetime Cohort (SJLIFE) study is to evaluate endocrine-related late effects and inform clinical practice by describing the implications of pituitary deficiencies among CCS through investigation of associations between hypopituitarism and specific health and quality-of-life outcomes. The aims of this study were to provide new information regarding the prevalence of growth hormone deficiency (GHD), luteinizing hormone/follicle-stimulating hormone

deficiencies (LH/FSHD), thyroid-stimulating homrone deficiency (TSHD), and adrenocorticotropic hormone deficiency (ACTHD) in a large population of long-term CCS treated with CRT; the associated risk factors; and the association between untreated deficiencies and cardiovascular health, bone mineral density (BMD), exercise tolerance, and frailty, a phenotype associated with increased risk for morbidity and mortality.[8,9]

PATIENTS AND METHODS

SJLIFE Study

Participants were enrolled onto the institutional review board–approved SJLIFE protocol.[10] Eligibility criteria included ≥ 10 years after diagnosis of childhood cancer, treatment at St Jude Children's Research Hospital, and age ≥ 18 years. The order of recruitment of eligible survivors was randomly determined by allocating patients to blocks of 50 patients. The current analysis of pituitary dysfunction was restricted to SJLIFE participants exposed to CRT and who did not have a tumor with direct mass effect on the hypothalamus or pituitary. Eligible patients were invited to return to St Jude Children's Research Hospital for clinical evaluations (performed from 2007 to 2012) in accordance with the Children's Oncology Group screening guidelines[11] augmented with a core laboratory battery, a physical performance assessment, and questionnaires that detail demographic information, medical/reproductive histories, quality of life, and health habits. All retrospective and prospective data in the current report were collected under the SJLIFE protocol (Fig 2). A history of previously diagnosed pituitary deficiencies was extracted from the medical record. The presence of a pituitary deficiency at the time of the SJLIFE evaluation was investigated using a morning blood sample in individuals who were not receiving medications that could interfere with laboratory results (eg, oral contraceptives or hormone replacement therapies). In individuals receiving such medications, none of which were interrupted at SJLIFE, the diagnosis of a pituitary deficiency was solely based on medical history assuming that previous diagnoses were valid and persistent. CRT was quantified by the maximum tumor prescribed dose to the brain. Markers of cardiovascular health, BMD, and physical fitness were measured at the time of the SJLIFE evaluation.

Assessment of Anterior Pituitary Functions

A fasting blood sample was collected at 8:00 am for the measurement of plasma insulin-like growth factor-1 (IGF-1), luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone (males), estradiol (females), thyroid-stimulating hormone (TSH), free thyroxine, and cortisol using electrochemiluminescent immunometric assays (Roche Cobas 6000 analyzer; Roche Diagnostics, Indianapolis, IN). Results were interpreted in relation to normative ranges and/or practice guidelines. IGF-1 was expressed as *z* scores with respect to sex and chronologic age. IGF-1 *z* scores less than −2 was a surrogate for adult GHD.[12] In males, LH/FSHD was diagnosed if total testosterone less than 200 ng/dL coincided with LH less than 7 IU/L and FSH less than 9.2 IU/L. In amenorrheic women less than 40 years old, estradiol less than 17 pg/mL and FSH less than 11.2 IU/L were considered indicative of LH/FSHD. TSHD was diagnosed when free thyroxine less than 0.9 ng/dL coincided with thyroid-stimulating hormone less than 4 mIU/L. An 8:00 am cortisol level of less than 5 μg/dL was suggestive of ACTHD. Because dynamic

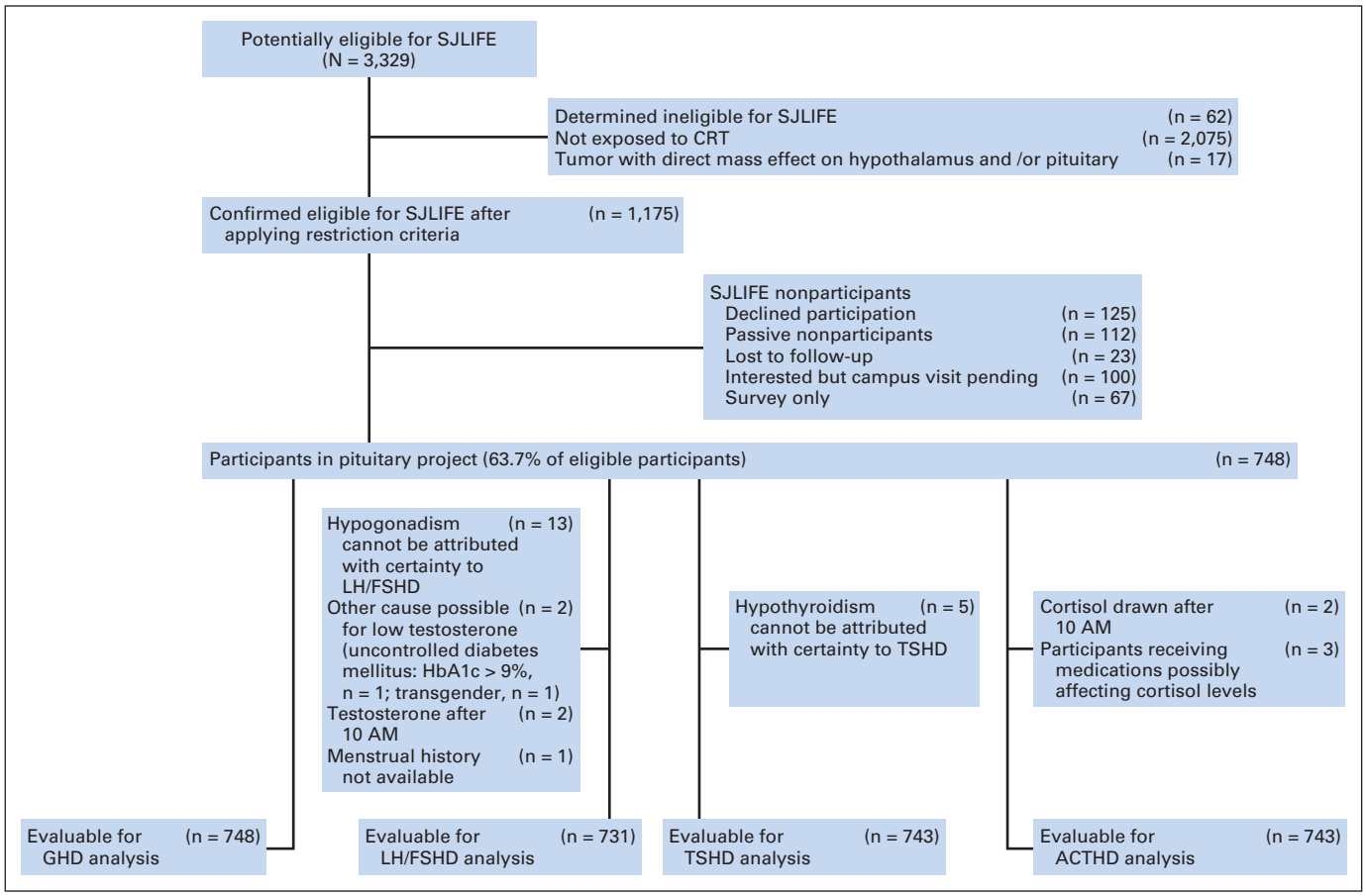

Fig 1. CONSORT diagram. ACTHD, adrenocorticotropic hormone deficiency; CRT, cranial radiotherapy; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; SJLIFE, St Jude Lifetime study; TSHD, thyroid-stimulating hormone deficiency.

testing was not available and given the limitations in using baseline IGF-1 and 8:00 am cortisol levels to define GHD and ACTHD respectively, we have referred to our prevalence findings for these outcomes as estimates.[12,13] Previously unknown pituitary deficiencies diagnosed through participation in SJLIFE were described as uncovered by systematic screening. Individuals with a known history of a pituitary deficiency but who were not receiving replacement therapy for it at SJLIFE and those with a deficiency uncovered by systematic screening were described as having an untreated deficiency. Patients whose hormonal deficiencies could not be attributed with certainty to a pituitary origin and those with missing outcome information or inadequate laboratory collection times were excluded.

Cardiovascular Health

All patients had measurements of height, weight, abdominal circumference, and resting blood pressure. Waist circumference was obtained with a Gulick tape measure,[14] and height and weight were measured using a stadiometer and an electronic scale (Scale-Tronix, White Plains, NY), respectively. Body-mass index (BMI) was calculated as weight in kilograms/(height in meters)^2. Abdominal obesity was defined by a waist circumference $\geq$ 102 cm in males or $\geq$ 88 cm in females and by a waist-to-height ratio of more than 0.5.[15] Blood pressure was evaluated after 5 minutes of quiet sitting, and hypertension was defined by systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg. Glucose, triglycerides, and high-density lipoprotein were measured using an enzymatic spectrophotometric assay (Roche Modular P Chemistry Analyzer; Roche Diagnostics). Fasting glucose $\geq$ 100 mg/dL and/or treatment with glucose-lowering medications were considered indicative of abnormal glucose levels. Dyslipidemia was defined by fasting total cholesterol $\geq$ 200 mg/dL, low-density lipoprotein $\geq$ 130 mg/dL, high-density lipoprotein less than 40 mg/dL ($<$ 50 mg/dL in women), and/or triglycerides $\geq$ 150 mg/dL.[16]

BMD

BMD was assessed using quantitative computed tomography with GE VCT LightSpeed 64-detector (GE Healthcare, Waukesha, WI) and Mindways quantitative computed tomography calibration phantoms and software (Mindways, Austin, TX). Average volumetric trabecular BMD for lumbar vertebrae L1 and L2 was calculated and reported as age- and sex-specific z scores. Low BMD was defined as a z score less than -2.[17]

Frailty

Physical performance was evaluated by characterizing individuals as meeting or not meeting criteria for physiologic frailty, a phenotype previously defined as including three or more of the following: low muscle mass, self-reported exhaustion, low energy expenditure, slow walking speed, and muscle weakness (Appendix Table A1, online only).[8] Appendicular mass values (kilograms) from dual x-ray absorptiometry were divided by height in meters squared, and low muscle mass was defined as values at least 1.5 standard deviations below age- and sex-specific reference values.[18] Scores 1.3 standard deviations below the population mean on the Vitality subscale of the Medical Outcomes Survey Short Form-36 were used to classify exhaustion.[19] The National Health and Nutrition Examination Survey Physical Activity Questionnaire was used to calculate energy expenditure.[20,21] Low energy expenditure was defined as less than 383 kcal/wk in men and less than 270 kcal/wk in women.[8] Walking speed was calculated based on the time to cover a distance of 15 ft. Women less than 159 cm and men less than 173 cm tall were classified as slow if they took $\geq$ 7 seconds; women $\geq$ 159 cm and men $\geq$ 173 cm tall were classified as slow if they took $\geq$ 6 seconds.[8] Hand grip strength (kilograms) was measured using a Jamar dynamometer (Preston-Sammons, Nottinghamshire, United Kingdom), and weakness was classified by sex- and BMI-specific cut points.[8]

Exercise Tolerance

The 6-minute walk test was used to evaluate exercise tolerance.[22] Poor exercise tolerance was defined by less than 400 m of distance covered in 6 minutes.[23]

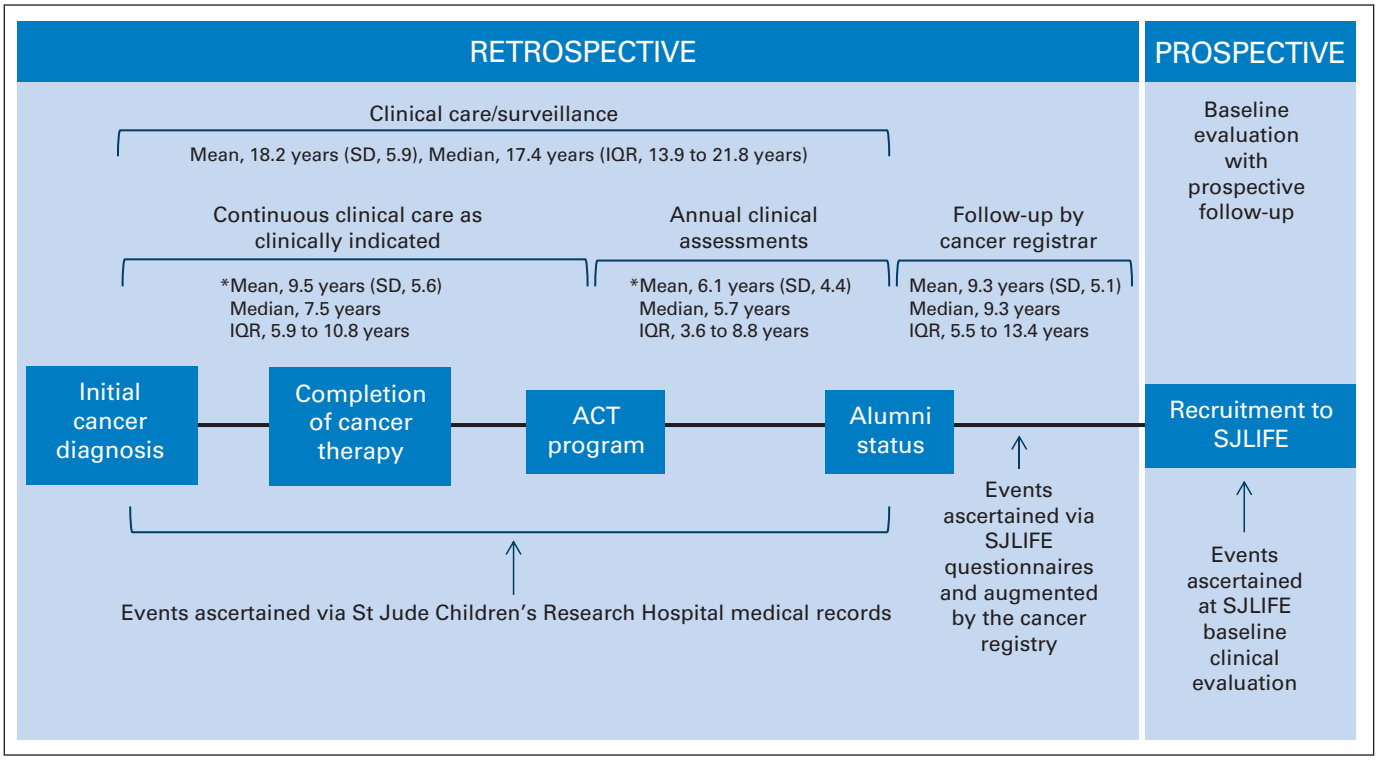

Fig 2. Summary of the St Jude Lifetime (SJLIFE) study design relative to retrospective and prospective ascertainment of pituitary dysfunction. (*) Subgroup of patients participating in the After Completion of Therapy (ACT) Program initiated in 1984. IQR, interquartile range; SD, standard deviation.

Statistics

Statistical considerations for the design and analytic approach are provided in the Appendix and Appendix Tables A2 to A5 (online only). Descriptive statistics included point prevalence, defined as the proportion of survivors with hypopituitarism at their clinical assessment. The associations between GHD, LH/FSHD, TSHD, or ACTHD and sex, ethnicity, age at diagnosis, age at exposure to CRT, CRT dose, time since the primary diagnosis and since exposure to CRT, and age and BMI at the time of the SJLIFE assessment were first tested in univariable models using χ^2 or Fisher's exact tests. Variables with $P \leq .1$ from the univariable analysis were included in multivariable logistic regression models to determine independent associations with GHD, LH/FSHD, TSHD, and ACTHD as distinct outcomes. Cumulative incidence was calculated using the Kaplan-Meier method[24] and assigning the date of detection of an outcome as the date of occurrence and censoring patients without an event at last follow-up (Appendix). Associations between untreated hormone deficiencies and cardiovascular health, BMD, measures of frailty, and exercise tolerance were also tested first in univariable and then in multivariable logistic regression models. Analyses did not include adjustment for multiple comparisons. SAS version 9.2 (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Study Population

Among 1,175 eligible patients, 748 (63.7%) completed enrollment in the first 68 recruitment blocks by April 30, 2012 (Fig 1), which provided a sufficient sample size and corresponding statistical power to evaluate specific aims relating to the presence of and risk factors for hypopituitarism. Compared with nonparticipants, participants were more likely to be white (Table 1). The mean age was 34.2 years (range, 19.4 to 59.6 years), and the mean time since primary cancer diagnosis was 27.3 years (range, 10.8 to 47.7 years). Participants were treated with CRT at a mean age of 7.6 years (range, 0.1 to 26.0 years).

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Participants (n = 748) No.	%	Nonparticipants (n = 427) No.	%	P
Sex					.12
Male	394	52.7	245	57.4	
Female	354	47.3	182	42.6	
Ethnicity					.01
White non-Hispanic	655	87.6	349	81.7	
Black non-Hispanic	77	10.3	57	13.4	
Other	16	2.1	21	4.9	
Current smoker status					–
No	606	81.0	—	—	
Yes	142	19.0	—	—	
Primary diagnosis					.09
Leukemia	543	72.6	296	69.3	
Lymphoma	33	4.4	31	7.3	
CNS tumor	90	12.0	60	14.1	
Embryonal	30	4.0	22	5.2	
Bone and soft tissue sarcoma	38	5.1	14	3.3	
Carcinoma	11	1.5	2	0.5	
Other	3	0.4	2	0.5	
Age at St Jude Lifetime evaluation, years					—
18-25	123	16.4	—	—	
26-35	326	43.6	—	—	
36-45	247	33.0	—	—	
≥ 46	52	7.0	—	—	
CRT dose, Gy					.28
1-14.9	40	5.3	28	6.6	
15-21.9	208	27.8	104	24.4	
22-29.9	316	42.3	182	42.6	
30-39.9	31	4.1	28	6.6	
≥ 40	153	20.5	85	19.9	
Time since CRT, years					—
< 15	48	6.4	—	—	
15-19	114	15.2	—	—	
20-24	186	24.9	—	—	
25-29	138	18.5	—	—	
≥ 30	262	35.0	—	—	
Age at CRT, years					.97
0-4	301	40.2	175	41.0	
5-9	223	29.8	122	28.6	
10-14	137	18.3	81	19.0	
≥ 15	87	11.6	49	11.5	

Abbreviation: CRT, cranial radiotherapy.

Point Prevalence and Risk Factors

Overall, 371 (51.4%; 95% CI, 47.7% to 55.1%) of 722 participants in whom all four anterior pituitary outcomes could be determined had at least one deficiency. Two hundred ninety-two patients (40.4%; 95% CI, 36.8% to 44.1%) had one deficiency, and 79 patients (10.9%; 95% CI, 8.8% to 13.5%) had multiple deficiencies. Figure 3 summarizes the relative proportions and overlap between the anterior pituitary deficiencies.

GHD

Among 748 individuals treated with CRT, 348 had an IGF-1 z score less than −2, providing a GHD prevalence estimate of 46.5% (95% CI, 42.9% to 50.2%), with estimates of 47.5% (95% CI, 43.8% to 51.3%) and 30.2% (95% CI, 17.2% to 46.1%) after exposure to CRT doses ≥ 18 Gy and less than 18 Gy, respectively ($P = .03$). The diagnosis of GHD was newly established in 212 participants (60.9% of patients with GHD; 95% CI, 55.6% to 66.1%). Age ≥ 10 years at CRT and age ≥ 36 years at the time of the SJLIFE assessment were associated with lower odds of GHD when compared with age less than 5 years at CRT and age less than 26 years at SJLIFE assessment, respectively; CRT doses of 22 to 29.9 Gy were associated with higher odds of GHD compared with CRT doses less than 22 Gy (Table 2).

LH/FSHD

Of 731 participants for whom LH/FSHD could be assessed, 79 patients (10.8%; 95% CI, 8.6% to 13.3%) had results consistent with this deficiency. The prevalence of LH/FSHD was 22.7% (95% CI, 16.2% to 30.2%) and 7.8% (95% CI, 5.7% to 10.2%) after CRT doses ≥ 40 Gy and less than 40 Gy, respectively ($P < .001$). The diagnosis was newly established in 46 individuals (58.2% of patients with LH/FSHD). Although roughly equal numbers of men and women had known LH/FSHD before SJLIFE (17 women v 16 men), most of those diagnosed through SJLIFE were men (34 men v 12 women). Male sex, white race, CRT dose ≥ 22 Gy ($v <$ 22 Gy), and BMI ≥ 30 kg/m^2 ($v <$ 25 kg/m^2) were associated with higher odds of LH/FSHD (Table 2).

TSHD

Fifty-six (7.5%; 95% CI, 5.7% to 9.7%) of the 743 evaluable participants had TSHD. This was newly diagnosed at SJLIFE in eight

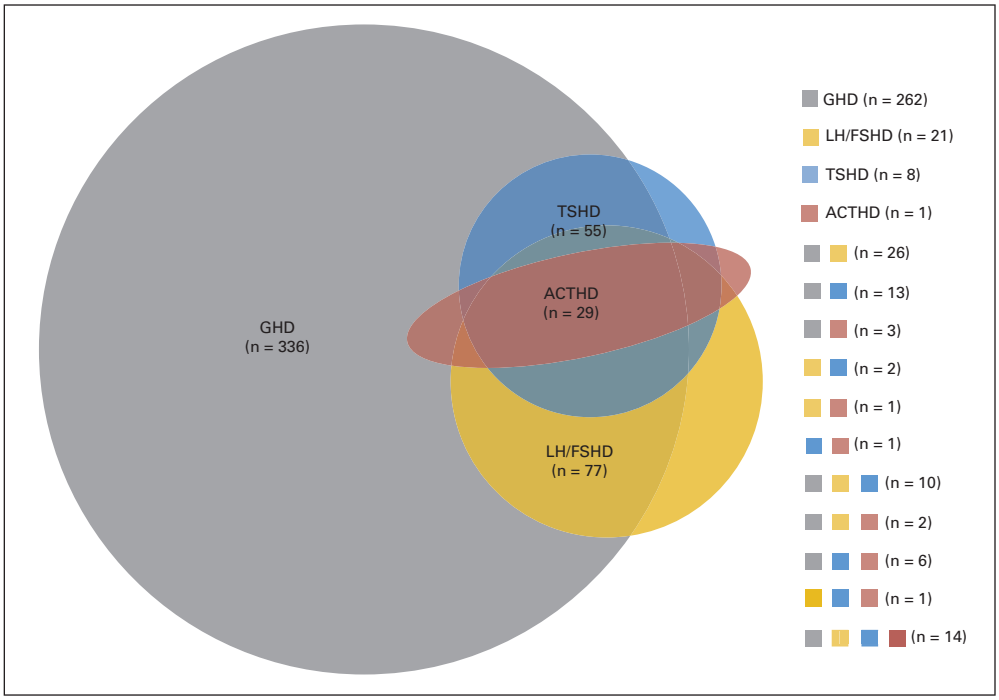

Fig 3. Relative proportions and overlap among anterior pituitary deficiencies following cranial radiotherapy. ACTHD, adrenocorticotropic hormone deficiency; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; TSHD, thyroid-stimulating hormone deficiency.

participants (14.3% of TSHD diagnoses). The prevalence of TSHD was 18.2% (95% CI, 12.4% to 25.4%) and 4.9% (95% CI, 3.3% to 6.9%) following CRT doses ≥ 40 Gy and less than 40 Gy respectively ($P < .001$). White race, age less than 26 years at SJLIFE assessment, and CRT dose ≥ 30 Gy ($v < 22$ Gy) were independently associated with higher odds of TSHD (Table 2).

ACTHD

ACTHD, proven by stimulation testing, was diagnosed in 29 individuals (3.9%; 95% CI, 2.6% to 5.6%) before SJLIFE. Only one new case of possible ACTHD was identified (3.3% of patients with ACTHD). The estimated prevalence of ACTHD was 4.0% (95% CI, 2.7% to 5.7%), with estimates of 13.3% (95% CI, 8.3% to 19.8%) and 1.7% (95% CI, 0.8% to 3.1%) at CRT doses of ≥ 40 Gy and less than 40 Gy, respectively ($P < .001$). Time since CRT less than 15 years ($v \geq 25$ years) and CRT dose ≥ 30 Gy ($v < 22$ Gy) were independently associated with higher odds of ACTHD (Table 2).

Cumulative Incidence Data

The estimated cumulative incidence at 40 years from cancer diagnosis is 72.4% (95% CI, 66.8% to 77.8%) for GHD, 24.4% (95% CI, 18.1% to 32.3%) for LH/FSHD, 11.6% (95% CI, 8.1% to 16.4%) for TSHD, and 5.2% (95% CI, 3.3% to 8.0%) for ACTHD (Appendix Fig A1, online only).

Untreated Deficiencies and Cardiovascular Health, BMD, Frailty, and Exercise Tolerance

Only one (0.3%) of 348 individuals with GHD and 17 (21.5%) of 79 individuals with LH/FSHD were receiving replacement therapy. To assess the impact of untreated GHD and/or LH/FSHD on outcomes related to cardiovascular health, BMD, frailty, and exercise tolerance, we excluded individuals whose pituitary status could not be determined for all four outcomes (n = 26), individuals with untreated TSHD (n = 8) or ACTHD (n = 1), and those on replacement therapy for GHD and/or LH/FSHD (n = 18). After applying these exclusions, 695 participants were available for this analysis.

Using a reference group of non-GHD individuals, the multivariable analysis supported independent associations between untreated GHD and increased waist-to-height ratio, low muscle mass, low energy expenditure, low hand grip strength, and poor exercise tolerance (Table 3). Using a reference group of non-LH/FSHD individuals, the multivariable analysis revealed independent associations between untreated LH/FSHD and increased waist circumference and waist-to-height ratio, hypertension, dyslipidemia, low BMD, slow walking speed, and poor exercise tolerance (Table 3).

DISCUSSION

This study provides a summary of the anterior pituitary deficits observed in what is, to date and to our knowledge, the largest and most comprehensive systematically assessed clinical cohort of long-term CCS exposed to CRT. With an average of 27 years of follow-up, novel findings include the identification of a substantial proportion of anterior pituitary deficiencies decades after exposure to CRT, especially GHD and LH/FSHD, and significant associations between untreated GHD and/or LH/FSHD and poor health outcomes.[8]

Strikingly large numbers of new cases of GHD were uncovered by systematic screening, which likely underestimate the true prevalence of GHD because IGF-1 measurements were used in lieu of dynamic testing.[25] The associations between untreated GHD and abdominal obesity, low muscle mass, low energy expenditure, muscle weakness, and poor exercise tolerance have been described in the adult population but not to the same extent in CCS.[26] Decreased lean mass, energy expenditure, and muscle strength are three of the five components of

Table 2. Risk Factors Associated With Anterior Pituitary Deficiencies: Results of Multivariable Analysis

	GHD (n = 748)					LH/FSHD (n = 731)					TSHD (n = 743)					ACTHD (n = 743)				
	Patients With Deficiency					Patients With Deficiency					Patients With Deficiency					Patients With Deficiency				
Factor	No.	%	OR	95% CI	*P*	No.	%	OR	95% CI	*P*	No.	%	OR	95% CI	*P*	No.	%	OR	95% CI	*P*
Sex	Not included in model										Not included in model					Not included in model				
Male						50	13.0	1.00												
Female						29	8.4	0.58	0.3 to 0.97	.04										
Ethnicity																Not included in model				
White	315	48.1	1.00			75	11.7	1.00			54	8.3	1.00							
Nonwhite	33	35.5	0.66	0.4 to 1.1	.09	4	4.4	0.28	0.1 to 0.8	.02	2	2.2	0.16	0.04 to 0.7	.01					
Age at CRT, years						Not included in model					Not included in model					Not included in model				
0-4	166	55.2	1.00																	
5-9	103	46.2	0.73	0.5 to 1.0	.09															
10-14	53	38.7	0.63	0.4 to 0.9	.03															
≥ 15	26	29.9	0.43	0.2 to 0.7	.002															
Age at SJLIFE, years						Not included in model										Not included in model				
18-25	62	50.4	1.00								21	17.4	1.00							
26-35	160	49.1	0.86	0.6 to 13	.51						22	6.8	0.37	0.2 to 0.8	.01					
≥ 36	126	42.1	0.51	0.3 to 0.9	.01						13	4.4	0.20	0.1 to 0.6	.004					
Time since CRT, years	Not included in model																			
< 15						9	18.8	1.00			8	16.7	1.00			8	17.0	1.00		
15-19						9	8.0	0.38	0.1 to 1.1	.08	12	10.7	0.70	0.2 to 2.0	.50	9	8.0	0.53	0.2 to 1.5	.24
20-24						17	9.4	0.77	0.3 to 2.0	.60	15	8.2	0.94	0.3 to 2.7	.91	8	4.3	0.41	0.1 to 1.2	.11
≥ 25						44	11.3	0.67	0.3 to 1.7	.40	21	5.3	0.88	0.3 to 2.9	.84	5	1.3	0.11	0.03 to 0.4	< .01
CRT dose, Gy																				
≤ 21.9	105	42.3	1.00			8	3.3	1.00			11	4.4	1.00			3	1.2	1.00		
22-29.9	172	54.4	1.99	1.4 to 2.9	< .01	32	10.3	3.02	1.3 to 7.0	.01	16	5.1	1.57	0.7 to 3.7	.30	6	1.9	2.93	0.7 to 12.5	.15
≥ 30	71	38.6	0.91	0.6 to 1.4	.64	39	21.6	9.71	4.2 to 22.3	< .01	29	16.2	4.46	2.1 to 9.7	< .01	21	11.6	8.81	2.5 to 30.9	< .01
Adjusted body-mass index, kg/m^2																Not included in model				
< 25	84	47.7	1.00			17	9.8	1.00			18	10.3	1.00							
25-29.9	87	39.7	0.69	0.5 to 1.0	.08	12	5.6	0.54	0.2 to 1.2	.14	9	4.1	0.53	0.2 to 1.3	.15					
≥ 30	177	50.1	1.00	0.7 to 1.5	.99	50	14.5	2.03	1.1 to 3.9	.03	29	8.3	1.35	0.7 to 2.7	.40					

NOTE. Variables with $P > .1$ from the univariable analysis were not included in the multivariable model.

Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; CRT, cranial radiotherapy; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; OR, odds ratio; SJLIFE, St Jude Lifetime study; TSHD, thyroid-stimulating hormone deficiency.

Table 3. Untreated GHD and LH/FSHD and Markers of Cardiovascular Health, Body Composition, and Physical Fitness: Results of Multivariable Analysis

	GHD					LH/FSHD				
Outcome Variable*	% of Patients With No Deficiency (n = 381)	% of Patients With Untreated Deficiency (n = 314)	OR†	95% CI	*P*	% of Patients With No Deficiency (n = 638)	% of Patients With Untreated Deficiency (n = 57)	OR*	95% CI	*P*
Increased waist circumference	39.1	45.6	1.26	0.93 to 1.72	.14	40.4	60.7	2.21	1.26 to 3.88	.01
Increased waist-to-height ratio	74.3	80.8	1.48	1.01 to 2.18	.04	75.8	92.9	3.39	1.19 to 9.66	.02
Hypertension	26.5	21.7	0.77	0.53 to 1.14	.19	22.7	42.1	1.98	1.07 to 3.65	.03
Elevated glucose	32.9	35.4	1.19	0.85 to 1.67	.32	33.0	45.6	1.20	0.66 to 2.17	.55
Dyslipidemia	61.7	60.8	0.94	0.69 to 1.28	.68	60.0	75.4	2.06	1.10 to 3.86	.02
Low BMD	5.8	10.3	1.78	0.99 to 3.18	.05	7.1	16.4	2.42	1.10 to 5.30	.03
Frailty	4.3	6.8	1.61	0.82 to 3.14	.17	5.1	9.1	1.75	0.65 to 4.70	.27
Low lean muscle mass	5.0	9.0	1.85	1.01 to 3.39	.05	6.6	8.8	1.25	0.47 to 3.31	.66
Exhaustion	25.7	27.4	1.05	0.74 to 1.48	.80	26.2	29.1	1.06	0.57 to 1.99	.85
Low energy expenditure	47.6	55.0	1.39	1.02 to 1.89	.04	49.9	62.5	1.58	0.89 to 2.80	.12
Slow walking speed	1.6	3.0	1.61	0.56 to 4.66	.38	1.6	8.9	5.58	1.82 to 17.12	.003
Muscle weakness	9.0	16.1	1.90	1.19 to 3.03	.01	11.7	17.9	1.50	0.72 to 3.11	.28
Poor exercise tolerance	5.7	11.8	2.11	1.16 to 3.81	.01	8.1	12.8	1.72	0.66 to 4.44	.27

Abbreviations: BMD, bone mineral density; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; OR, odds ratio.

*Increased weight circumference was defined by waist circumference ≥ 102 cm in men or ≥ 88 cm in women; the multivariable model included only GHD and LH/FSHD status. Increased waist-to-height ratio was defined by a ratio of > 0.5, with the multivariable model adjusted for age and race. Hypertension was defined by systolic blood pressure ≥ 140 or diastolic blood pressure DBP ≥ 90 mmHg, with the multivariable model adjusted for sex, body-mass index, race, and age. Elevated glucose was defined by fasting glucose level ≥ 100 mg/μL or treatment with glucose-lowering medications, with the multivariable model adjusted for sex, body-mass index, and age. Dyslipidemia was defined by fasting total cholesterol ≥ 200 mg/dL or high-density lipoprotein < 40 mg/dL or low-density lipoprotein ≥ 130 mg/dL or triglycerides ≥ 150 mg/dL among men and fasting total cholesterol ≥ 200 mg/dL or high-density lipoprotein < 50 mg/dL or low-density lipoprotein ≥ 130 mg/dL or triglycerides ≥ 150 mg/dL among women; the multivariable model included only GHD and LH/FSHD status. Very low BMD was defined by quantitative computed tomography BMD *z* score < −2. Quantitative computed tomography BMD *z* score was calculated with age- and sex-specific reference values; the multivariable model included only GHD and LH/FSHD status. Frailty was defined by ≥ three positive components among "low lean muscle mass," "exhaustion," "low energy expenditure," "slowing walking speed," and "muscle weakness"; the multivariable model included only GHD and LH/FSHD status. Low lean muscle mass was defined as dual-energy x-ray absorptiometry–derived lean mass values at least 1.5 standard deviations below the sex-, age-, and race-specific reference values; the multivariable model included only GHD and LH/FSHD status. Exhaustion was defined by Short Form–36 vitality score 1.3 standard deviations below the population mean of 50, with the multivariable model adjusted for sex, body-mass index, and age. Low energy expenditure was defined as < 383 kcal/week in men and < 270 kcal/week in women; the multivariable model only included GHD and LH/FSHD status. Women < 159 and men < 173 cm tall were classified as slow if they took ≥ 7 seconds to cover a distance of 15 feet, and women < 159 and men < 173 cm tall were classified as slow if they took ≥ 6 seconds to cover a distance of 15 feet; the multivariable model included only GHD and LH/FSHD status. Muscle weakness was defined as hand grip below sex- and body-mass index–specific cut points; the multivariable model included only GHD and LH/FSHD status. Poor exercise tolerance was defined as 6-minute walk distance < 400 m, with the multivariable model adjusted for sex, body-mass index, and race.

†OR comparing those with untreated deficiency with those with absent deficiency.

the frailty phenotype, which may predict early mortality.[8] The reported prevalence of frailty in SJLIFE was 13.1%, with a median age of 33.6 years, which is comparable to the rate observed in individuals age ≥ 65 years old (9.9%) in the general population.[9] The contribution of untreated GHD and whether growth hormone replacement can induce sustainable improvements in these outcomes are unknown.[27] GHD is the most common pituitary deficit after CRT. It occurred at relatively low doses of radiation,[1,6,7,28-30] was more likely after CRT at a young age, as described by some but not all authors,[29,31] and was less likely to be present in individuals ≥ 36 years old at SJLIFE, a finding possibly a result of the relatively young age of survivors of brain tumors in this cohort.[10] That the development of GHD occurs both in a dose- and time-dependent fashion was nevertheless highlighted in our findings of comparable risks among individuals treated with doses less than 22 Gy, such as acute lymphoblastic leukemia survivors exposed to prophylactic CRT decades ago, and much younger individuals surviving brain tumors treated with doses ≥ 30 Gy and who are likely to have been followed for a shorter period of time.[6]

A substantial proportion of individuals with LH/FSHD were diagnosed through systematic screening. Untreated LH/FSHD was independently associated with abdominal obesity, hypertension, dyslipidemia, low BMD, low energy expenditure, and slow walking. Given the difficulties in diagnosing LH/FSHD in obese adult men, it is unclear whether, in some instances, these associations are the result of, rather than the cause of, obesity.[32] The association of LH/FSHD with low BMD, however, likely reflects the known effect of decreased sex steroid levels on bone health in the adult population and hints at possible consequences on bone health regardless of the confounding effect of obesity.[33,34] Nevertheless, the balance between long-term risks and benefits of aggressively treating asymptomatic LH/FSHD in this population needs to be investigated further, especially in the context of naturally declining function in relation to aging.[35,36] The prevalence of LH/FSHD was second only to GHD.[5,7,37] As previously reported, LH/FSHD was associated with doses of CRT ≥ 22 Gy.[7,28,38,39] The significant associations with male sex and white race are novel and may reflect sex and genetic variations in susceptibility to radiation that deserve further study.

The proportion of new diagnoses of TSHD and ACTHD was much lower than for GHD and LH/FSHD. The prevalence of TSHD was within the range previously reported in two pediatric studies.[28,40] The estimated prevalence of ACTHD in SJLIFE was lower than rates previously reported (18% to 43% of tested individuals), most likely because of differences in population and in testing modalities.[13,28,41] Because we did not use dynamic testing, it is possible that we have

underestimated the number of ACTHDs.[13] Both TSHD and ACTHD were associated with CRT doses of more than 30 Gy, as previously observed.[7,28,37,38] Participants who were younger at SJLIFE and those assessed less than 15 years after CRT had higher odds of TSHD and ACTHD. This observation is possibly a consequence of the younger age of survivors of high-risk brain tumors in our cohort.[10] The significant association between white race and TSHD is novel, may reflect genetic variations in susceptibility to radiation, and deserves further study.

Study limitations include the reliance on plasma IGF-1 and 8:00 am cortisol levels instead of dynamic endocrine testing for GHD and ACTHD[12,13] and on the assumption that pre-existing hormonal deficits were valid and persistent at SJLIFE. Hypothalamic-pituitary dosimetry was not available on all SJLIFE participants; however, the majority of patients (89.2%) received only whole-brain RT, which does reflect the dose to the hypothalamic-pituitary axis. Findings from this study may nevertheless not be applicable to individuals treated for brain tumors with contemporary CRT regimens. Reliance on a combination of retrospective observational data and cross-sectional assessments for calculation of cumulative incidence may overestimate rates in later time intervals, while underestimating rates in the decade before the SJLIFE evaluation (Appendix). Lastly, adjustment for multiple comparisons was not performed, and thus, some of the positive results may be a result of chance.

Previously undiagnosed GHD, LH/FSHD, TSHD, and ACTHD may appear during adulthood in CCS treated with CRT. These findings underscore the importance of lifelong screening for anterior pituitary deficiencies in at-risk CCS.[7] They also call attention to the challenges and deficiencies in the medical care provided to these individuals as they age.[4] Interactions between pituitary dysfunction, sex, and ethnicity and the impact of untreated GHD and LH/FSHD on cardiovascular health, body composition, and physical fitness deserve further investigation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Anterior Hypopituitarism in Adult Survivors of Childhood Cancers Treated With Cranial Radiotherapy: A Report From the St Jude Lifetime Cohort Study

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Appendix

Calculations of Statistical Power to Address the Study Aims

The first consideration, before undertaking the current analysis, was to ensure that we had a participation rate of at least 60% and reasonable estimates of power to detect meaningful effects sizes for the primary outcomes of interest. Within the first 68 recruitment blocks of size 50 each, the overall participation rate was 63.7%. The four primary outcomes to be studied were growth hormone deficiency (GHD), luteinizing hormone/follicle-stimulating hormone deficiency (LH/FSHD), thyroid-stimulating hormone deficiency (TSHD), and adrenocorticotropic hormone deficiency (ACTHD), and of the 1,175 patients confirmed eligible for the St Jude Lifetime (SJLIFE) study (after applying restriction criteria), we had 748, 731, 743, and 743 evaluable patients for the four outcomes providing participation rates of 63.7%, 62.2%, 63.2%, and 63.2%, respectively. In addition, a priori, the hypothesis was that patients who receive higher doses of cranial radiotherapy (CRT) would have higher incidence of GHD, LH/FSHD, TSHD, and ACTHD abnormalities, and the sample size justification was based on detecting higher odds ratios in the group receiving higher doses of CRT. The cutoff values for the higher CRT dose for the four outcomes, based on literature, were $\geq$ 18 Gy for GHD and $\geq$ 40 Gy for LH/FSHD, TSHD, and ACTHD.

It is seen from Appendix Tables A2 to A5 that the power estimates for the three outcomes LH/FSHD, ACTHD, and TSHD were similar because the sample sizes were similar, providing reasonable power to detect an odds ratios of $\geq$ 2 with at least 80% power if the baseline rate of the abnormality was $\geq$ 15%. However, for GHD, we were only able to detect larger effect sizes when the baseline rates of abnormality were approximately $\geq$ 20%.

Thus, the rationale for conducting the analysis with the inclusion of 68 blocks was the fact that we had at least a 60% participation rate for all the four outcome measures of interest and we had reasonable power (for at least three outcome measures) for detecting higher odds with higher doses of CRT, which was of primary interest.

Consideration of Time to Occurrence Analyses Using Cumulative Incidence

On the basis of the design and data sources available for the SJLIFE cohort (summarized in Fig 2 in the article), the date of occurrence of events (ie, ascertainment through medical detection because of routine screening or through presentation of the survivor with clinical signs or symptoms) is known for each of the adverse outcomes within the study population (including pituitary dysfunction). All survivors who did not have the event of interest by the time they were observed at the baseline SJLIFE visit were censored at the time of their visit. However, a proportion of these adverse outcomes are diagnosed at the time of the SJLIFE baseline clinical visit when survivors are uniformly screened according to the SJLIFE protocol. This clinical screen will (to varying degrees) have a tendency to overestimate cumulative incidences for later follow-up time points.

The maximum observation time is the SJLIFE baseline visit, and the outcome is yes or no for pituitary dysfunction. The GHD outcome illustrates the most extreme example of how the SJLIFE assessment may impact time-specific cumulative incidences given that approximately 60% of GHDs were discovered as part of the SJLIFE baseline visit, whereas the remaining 40% of GHDs had been documented before SJLIFE, with date of clinical diagnosis obtained from medical records.

In observational clinical research, one is often confronted with methodologic challenges. Given the observational data available for the SJLIFE cohort, encompassing almost 50 years of follow-up for some participants, it is clear that we cannot calculate a true cumulative incidence rate for pituitary dysfunction. Thus, we adopted an approach that takes advantage of the full spectrum of information available and goes beyond just reporting point prevalence by applying an approach we used in the previous version of this article, as well as in earlier published work from SJLIFE, by describing cumulative incidence. Obviously, it is important to recognize these limitations and the potential implications for interpretation of the findings.

Table A1. Specific Criteria Used to Define Frailty in St Jude Lifetime Cohort

Frailty Component	St Jude Lifetime Cohort Criteria
Low lean muscle mass	Lean muscle mass by dual x-ray absorptiometry at least 1.5 standard deviations below age- and sex-specific reference values when compared with data from a national sample (NHANES)[18]
Self-reported exhaustion	Score ≤ 40 (1.3 standard deviations, based on a standard normal distribution; this represents approximately the lowest 6.7% of the general population) on the Vitality subscale of the Medical Outcomes Survey Short Form-36[19]
Low energy expenditure	Expended < 383 kcal/wk (men) or < 270 kcal/wk (women) during leisure time physical activity based on the NHANES Physical Activity Questionnaire[20,21]
Slowness	Women < 159 cm and men < 173 cm tall were classified as slow if they took ≥ 7 seconds, and women ≥ 159 cm and men ≥ 173 cm tall were classified as slow if they took ≥ 6 seconds to walk 15 ft at their usual pace[8]

	Hand Grip Strength Stratified by BMI and Sex[8]:			
	Men		Women	
Weakness	BMI (kg/m^2)	Cut Point (kg)	BMI (kg/m^2)	Cut Point (kg)
	≤ 24	≤ 29	≤ 23	≤ 17
	24.1-26	≤ 30	23.1-26	≤ 17.3
	26.1-28	≤ 30	26.1-29	≤ 18
	> 28	≤ 32	> 29	≤ 21

Abbreviations: BMI, body-mass index; NHANES, National Health and Nutrition Examination Survey.

Table A2. Power Estimates for the Given Sample Size and Hypothetical Effect Sizes for the Outcome of Growth Hormone Deficiency

	ψ = Odds Ratio									
P1	1.6	1.8	2.0	2.2	2.4	2.6	2.8	3.0	3.2	3.4
0.05	0.061	0.080	0.105	0.135	0.170	0.212	0.259	0.310	0.366	0.424
0.10	0.111	0.163	0.228	0.305	0.3892	0.477	0.564	0.647	0.721	0.785
0.15	0.159	0.243	0.342	0.449	0.555	0.655	0.741	0.813	0.868	0.910
0.20	0.203	0.311	0.432	0.553	0.663	0.757	0.831	0.886	0.925	0.952
0.25	0.241	0.366	0.499	0.623	0.729	0.813	0.875	0.919	0.949	0.968
0.30	0.271	0.408	0.546	0.669	0.769	0.844	0.898	0.935	0.959	0.974

NOTE. N1 (< 18 Gy) = 43 and N2 (≥ 18 Gy) = 705; P1 = proportion abnormal in the control group.

Table A3. Power Estimates for the Given Sample Size and Hypothetical Effect Sizes for the Outcome of Luteinizing Hormone/Follicle-Stimulating Hormone Deficiency

	ψ = Odds Ratio									
P1	1.6	1.8	2.0	2.2	2.4	2.6	2.8	3.0	3.2	3.4
0.05	0.186	0.288	0.407	0.531	0.649	0.751	0.833	0.893	0.935	0.962
0.10	0.345	0.528	0.698	0.828	0.913	0.960	0.983	0.994	0.998	0.999
0.15	0.472	0.685	0.842	0.932	0.975	0.992	0.998	0.999	1.000	1.000
0.20	0.565	0.779	0.908	0.968	0.991	0.996	0.999	1.000	1.000	1.000
0.25	0.631	0.834	0.940	0.982	0.995	0.999	1.000	1.000	1.000	1.000
0.30	0.676	0.866	0.956	0.988	0.997	0.999	1.000	1.000	1.000	1.000

NOTE. N1 (< 40 Gy) = 581 and N2 (≥ 40 Gy) = 150; P1 = proportion abnormal in the control group.

Table A4. Power Estimates for the Given Sample Size and Hypothetical Effect Sizes for the Outcome of Adrenocorticotropic Hormone Deficiency

	ψ = Odds Ratio									
P1	1.6	1.8	2.0	2.2	2.4	2.6	2.8	3.0	3.2	3.4
0.05	0.186	0.289	0.408	0.532	0.650	0.753	0.834	0.894	0.936	0.963
0.10	0.346	0.530	0.700	0.830	0.914	0.961	0.984	0.994	0.999	0.999
0.15	0.473	0.687	0.843	0.933	0.975	0.992	0.998	0.999	1.000	1.000
0.20	0.567	0.780	0.909	0.969	0.991	0.998	0.999	1.000	1.000	1.000
0.25	0.633	0.835	0.941	0.982	0.996	0.999	1.000	1.000	1.000	1.000
0.30	0.678	0.867	0.956	0.988	0.997	0.999	1.000	1.000	1.000	1.000

NOTE. N1 (< 40 Gy) = 593 and N2 (≥ 40 Gy) = 150; P1 = proportion abnormal in the control group.

Table A5. Power Estimates for the Given Sample Size and Hypothetical Effect Sizes for the Outcome of Thyroid-Stimulating Hormone Deficiency

	ψ = Odds Ratio									
P1	1.6	1.8	2.0	2.2	2.4	2.6	2.8	3.0	3.2	3.4
0.05	0.184	0.285	0.403	0.527	0.645	0.747	0.830	0.891	0.934	0.961
0.10	0.342	0.525	0.695	0.826	0.911	0.959	0.983	0.994	0.998	0.999
0.15	0.469	0.682	0.839	0.931	0.974	0.992	0.998	0.999	1.000	1.000
0.20	0.562	0.776	0.906	0.967	0.990	0.997	0.999	1.000	1.000	1.000
0.25	0.628	0.832	0.939	0.981	0.995	0.999	1.000	1.000	1.000	1.000
0.30	0.673	0.864	0.955	0.987	0.997	0.999	1.000	1.000	1.000	1.000

NOTE. N1 (< 40 Gy) = 595 and N2 (≥ 40 Gy) = 148; P1 = proportion abnormal in the control group.

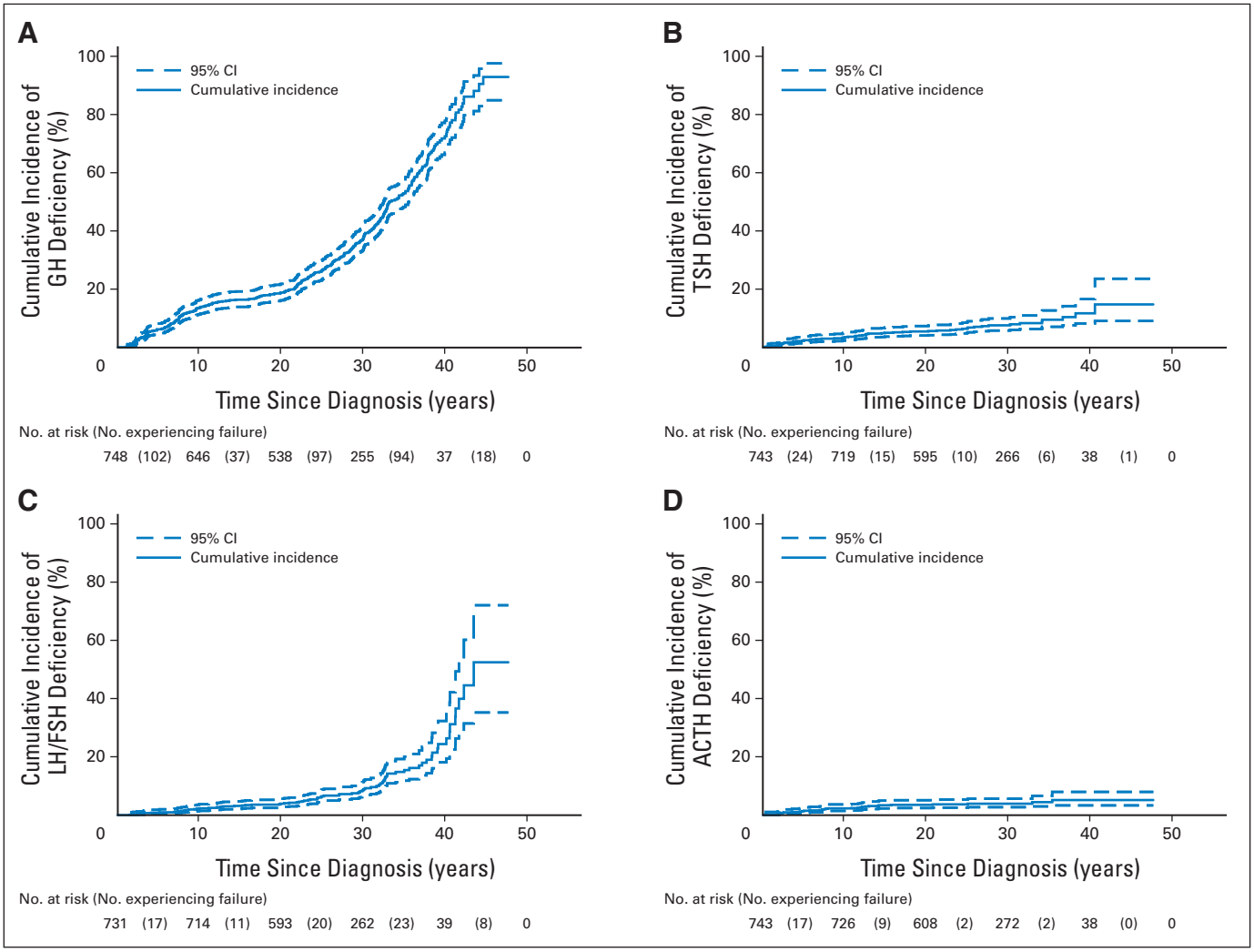

Fig A1. Cumulative incidence of (A) growth hormone (GH) deficiency, (B) thyroid-stimulating hormone (TSH) deficiency, (C) luteinizing hormone/follicle-stimulating hormone (LH/FSH) deficiency, and (D) adrenocorticotropic hormone (ACTH) deficiency from cancer diagnosis.